Innovations in the Radiotherapy of Non–Small Cell Lung Cancer

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Background: This review was performed to describe recent innovations in the radiation therapy of lung cancer.

Methods: The literature was reviewed regarding recent research in the therapy of lung cancer. Emphasis was placed on newer radiation therapy (RT) techniques.

Results: Advances in physics and computer technology have improved radiation delivery systems. New strategies have been used, such as altered fractionation patterns, three-dimensional treatment planning, intensity-modulated RT (IMRT), tomotherapy, stereotactic RT, and heavy ion RT. New technologies will make it possible to administer higher doses more precisely, which should result in better disease control, with less toxicity.

Conclusion: Further research will improve the outcome of patients with lung cancer by providing more effective tools for the RT of this disease.

Key Words: Lung cancer, Radiation therapy, New technology, Heavy ion therapy, Intensity-modulated radiation therapy, Stereotactic radiotherapy, Tomotherapy, CyberKnife.

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Lung cancer is the leading cause of cancer deaths, having caused an estimated 1.18 million deaths worldwide in 2002.[1] In the United States alone, lung cancer resulted in an estimated 173,770 deaths in 2004.[2] Although currently available therapies cannot cure most patients, there have been improvements in the outcome over time.[3]

The standard treatment for locally advanced inoperable lung cancer used to be radiation therapy (RT) alone. The Radiation Therapy Oncology Group (RTOG) performed a phase III trial to evaluate the influence of dose on outcome and compared 40 Gy in 20 daily fractions, 50 Gy in 25 fractions, and 60 Gy in 30 fractions. The radiographically determined local failure rates were 48% with 40 Gy, 38% with 50 Gy, and 27% with 60 Gy. Although the differences in survival were not significant, this study was used to define the standard RT dose in the United States as 60 Gy in 30 daily fractions.[4] Conventional RT alone resulted in a median survival of 10 months and a 5-year survival of 5%.

Phase III trials have demonstrated a survival advantage for the addition of chemotherapy to RT for non–small-cell lung cancer (NSCLC). The Cancer and Leukemia Group B reported that induction chemotherapy (cisplatin plus vinblastine) followed by conventional RT (60 Gy in 30 fractions) yielded significantly better survival than conventional RT alone. The median and 5-year survivals were 13.7 months and 17% for the combined therapy versus 9.6 months and 6% for RT alone ($p = 0.012$).[5] Additional phase III trials revealed that the combination of cisplatin-based chemotherapy plus RT produced better survival rates than RT alone.[6–9]

Dose-Fractionation Studies

Randomized prospective studies have failed to demonstrate an advantage for twice-daily radiotherapy (BIDRT) compared with once-daily radiotherapy (QDRT) for stage III NSCLC. The RTOG and North Central Cancer Group (NCCTG) studies (RTOG 9410 and NCCTG 94-24-52) compared chemotherapy plus either BIDRT or QDRT and failed to show an advantage for BIDRT.[10,11] In addition, both RTOG 9410 and a study reported by Furuse et al. revealed significantly improved survival with the use of concurrent RT plus chemotherapy as opposed to sequential therapy.[12]

Three-times-per-day RT (TIDRT) has shown promise for NSCLC. Saunders et al. performed a randomized study that compared QDRT (60 Gy in 30 fractions over 6 weeks) with continuous hyperfractionated accelerated RT (CHART) (54 Gy in 36 fractions three times per day over 12 days).[13] No chemotherapy was administered. Patients receiving CHART had a 2-year survival of 29% versus 20% for those that received QDRT ($p = 0.008$). These findings demonstrate the critical importance of treatment time on radiotherapy outcome. CHART was delivered in only 12 days, whereas the BIDRT programs used in NCCTG 94-24-52 and RTOG 9410 were approximately 6 weeks long. Accelerated repopulation of tumor cells during radiotherapy occurred to a lower degree during CHART, yielding more favorable results.

The Eastern Cooperative Oncology Group initiated a phase III trial (E-2597) of chemotherapy (two cycles of paclitaxel plus carboplatin) followed by either QDRT (64 Gy in 32 fractions over 6.5 weeks) or TIDRT (57.6 Gy in 36 fractions over 12 weekdays) for stage III NSCLC.[14] Unfortunately, accrual was slow and the study was closed before

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completion. The median survival was 14.9 months with QDRT versus 20.3 months with TIDRT.

Mayo Clinic investigators performed a trial with 20 patients treated with escalating doses of daily cisplatin administered concurrently with the same regimen of TIDRT used in the Eastern Cooperative Oncology Group trial. The median survival was 22 months and 5-year survival was 25%.[15] TIDRT appears to be a promising technique for unresectable NSCLC based on these trials.

Following RT and chemotherapy, the local control rates based on radiographic studies appear to be substantially better than those based on pathologic findings. Le Chevalier et al. performed a trial comparing RT (65 Gy) alone versus RT plus chemotherapy. Patients underwent serial bronchoscopic biopsies and were found to have local control rates at 1 year of only 15% with RT alone and 17% with combined modality therapy.[16] This finding suggests that local control rates achieved with RT plus chemotherapy are generally unsatisfactory. Based on the poor local control rates and dose–response data, Mehta et al. estimated that it would take a dose of approximately 85 Gy to achieve a 50% long-term control rate using standard 2-Gy daily fractions.[17] It appears that higher doses and/or shorter treatment times would be required to achieve better disease control. Technologies that could be helpful in accomplishing these goals include the use of three-dimensional planning, intensity-modulated RT (IMRT), tomotherapy, stereotactic RT, and charged heavy particle RT.

Three-Dimensional Treatment Planning and Dose Escalation

Investigators have performed dose-escalation studies using three-dimensional treatment planning.[18–23] Three-dimensional planning systems allow one to create beams from any angle to treat a tumor. Complex treatment plans with carefully chosen fields can be used to deliver greater than standard doses while respecting the tolerance of the normal tissues.[24] In addition, there are tools available in three-dimensional treatment planning systems that can ensure appropriate coverage of the intended target. This was an important advance, as targeting errors occurred in up to 31% of patients on cooperative group trials before the three-dimensional imaging era.[25]

One major shift in treatment strategy was the irradiation of gross disease without prophylactic nodal RT. There were several reasons for this shift in philosophy. The dose of radiation commonly used (60 Gy in 30 fractions) was not enough to sterilize bulky epithelial tumors. Simply increasing the dose delivered to the large volumes of the chest included when irradiating lymph nodes prophylactically was believed to cause unacceptable toxicity. In addition, irradiating clinically uninvolved nodal areas prophylactically did not appear rational when the gross tumor was infrequently controlled.

Many of the patients treated in the earlier dose-escalation trials received no chemotherapy or, in some cases, sequential therapy. Doses of RT administered have ranged up to 103 Gy for smaller tumors. Investigators in Michigan, Rotterdam, and New York reported favorable results with 18- to 21-month median survival.[19,22,23] In addition, isolated nodal failures in untreated areas were infrequent (0–6.5%).[19,22,23]

Rosenzweig et al. summarized the findings of the Memorial Sloan-Kettering Cancer Center, University of Michigan, and RTOG trials.[25] They divided the tumors by size in this evaluation of these dose-escalation studies. Small tumors were peripheral coin lesions for which RT required a V20 (volume of total lung receiving ≥20 Gy) of less than 25%. Intermediate tumors were those 4 cm or larger with hilar or limited mediastinal adenopathy. Large tumors were those with massive thoracic and mediastinal disease. The maximum dose administered in various trials ranged from 84 to 102.9 Gy for small tumors, 75.6 to 84 Gy for medium tumors, and 65.1 to 84 Gy for large tumors. The maximum tolerated dose (MTD) was 83.8 (RTOG 9311) to 84 (Memorial Sloan-Kettering Cancer Center) Gy for smaller tumors, 77.4 Gy for intermediate sized tumors (RTOG 9311), and 65.1 Gy for the larger tumors (University of Michigan).

One important concern is the lack of correlation between acute and chronic toxicity. Acute toxicity is the endpoint used in most phase I trials, but chronic RT toxicity may be of greater concern in terms of patient outcome. A recent update of RTOG 9311 reported late lung toxicity in 15% of patients with a V20 of less than 25% who received a total dose of 77.4 Gy or higher and in those with a V20 of between 25% and 37% and who received a total dose of 70.9 Gy or higher.[18] Higher values of V20 have been correlated with increased risk of pneumonitis.[26,27]

Recently, Socinski et al. reported a phase I trial that included induction chemotherapy (carboplatin, irinotecan, and paclitaxel) followed by concurrent chemotherapy (carboplatin and paclitaxel) and RT.[28] The RT used in this study contrasted with the other three-dimensional dose escalation trials because it included prophylactic nodal RT during the initial weeks of RT. In spite of the inclusion of prophylactic nodal RT and concurrent chemotherapy, they were able to boost gross disease to 90 Gy and concluded that this was safe based on acute toxicity. However, significant chronic toxicity did occur in three of the six patients that received 90 Gy, which included one grade 2 esophageal stricture, one grade 3 pneumonitis, and one grade 5 hemoptysis. The median survival was quite favorable at 24 months.

Recent three-dimensional RT dose-escalation studies targeted gross disease alone and included concurrent chemotherapy. Two separate phase I trials, one performed by the RTOG (L-0117) and the other performed by NCCTG (N0028), determined that 74 Gy in 37 daily fractions was the MTD when administered with concurrent weekly carboplatin and paclitaxel.[29,30] Figures 1 and 2 show the dosimetry of a patient treated with 74 Gy in 37 fractions on NCCTG trial N0028.

Intensity-Modulated RT

IMRT uses multiple beamlets of varying intensity within each radiation field. Planning is generally performed with inverse planning systems and delivered with dynamic multileaf collimators that vary the field shape actively during RT. The multileaf collimators are computer-guided motorized metal blades that extend into the radiation field and act

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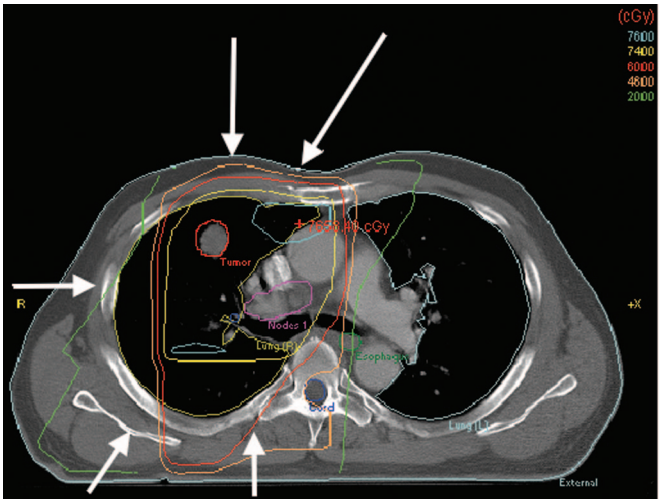

FIGURE 1. Dosimetry from a plan for a patient treated on NCCTG trial N0028. Tumor and adenopathy are encompassed within 74 Gy isodose (*yellow*). The five beams were composed of 6-MV x-rays directed in the direction of the five *arrows*. The isodose lines shown include the following: 76 Gy (*blue*), 74 Gy (*yellow*), 60 Gy (*red*), 46 Gy (*beige*), and 20 Gy (*green*).

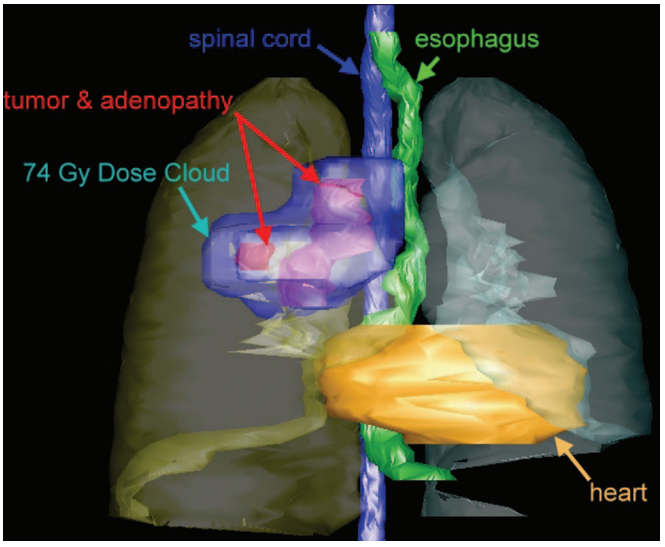

FIGURE 2. Three-dimensional reconstruction of a plan for the patient treated on NCCTG trial N0028 shown in Figure 1. The tumor and adenopathy (*pink*) are encompassed in the 74 Gy isodose cloud (*blue*). The other structures include the spinal cord (*blue*), the esophagus (*green*), the heart (*orange*), the left lung (*gray*), and the right lung (*yellow*).

as blocks. They move constantly during the IMRT to modulate the intensity of the beam. Inverse planning is performed with sophisticated computer algorithms that allow the user to prescribe specific radiation dose parameters for individual structures. Then, the computer creates the beams to accomplish these goals. This is in contrast to standard forward RT planning, which is accomplished by placing a number of beams into the planning system and allowing the computer to calculate the outcome in terms of dose distribution.

M. D. Anderson Cancer Center investigators performed dosimetric studies comparing three-dimensional plans to IMRT plans. The IMRT plans were associated with better tumor coverage and sparing of normal tissues. They prescribed 63 Gy to 95% of the planning target volume. The planning target volume includes both gross and microscopic disease but also accounts for movement and uncertainty. IMRT was associated with a median reduction in the volume of lung receiving greater than or equal to 20 Gy (V20) of 10% with IMRT compared with three-dimensional treatment planning[31,32] (Figures 3 and 4).

Holloway et al. performed a phase I trial of neoadjuvant chemotherapy (carboplatin plus either paclitaxel or vinorelbine) followed by IMRT, 84 Gy in 35 daily fractions (2.4 Gy/fraction).[33] One of the first five patients developed grade 5 toxicity and the trial was closed. It appears that this was too high a starting dose for a phase I trial. More conservative IMRT dose escalation studies are needed to define whether this technology can deliver higher than standard doses of RT safely.

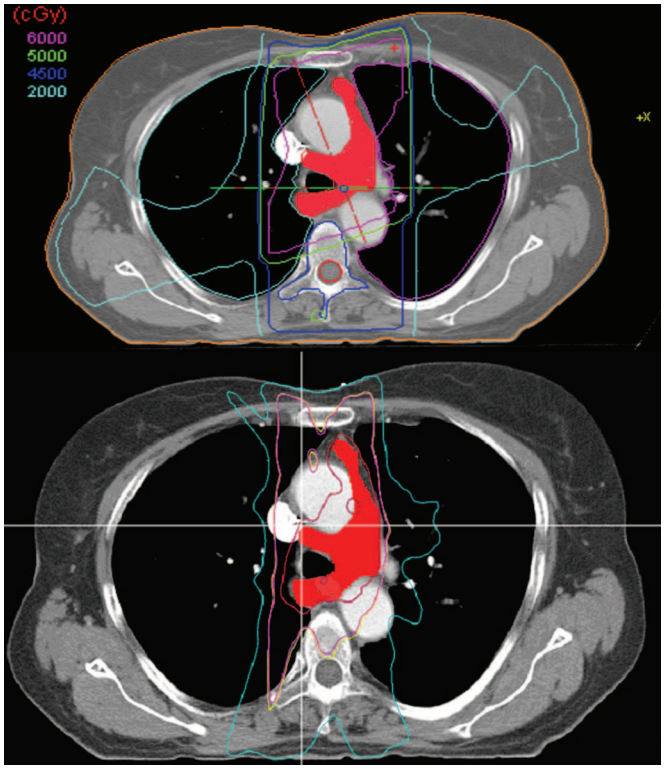

FIGURE 3. Conventional RT plan (*top*) using anteroposterior-posteroanterior, and opposed oblique fields followed by an IMRT treatment plan (*bottom*) using a nine-field approach. Both plans deliver 60 Gy (*purple isodose line*) to the tumor (*red*), but the volume of lung receiving 20 Gy or greater (V20 = volume encompassed by the *light blue isodose lines*) is dramatically smaller in the IMRT plan.

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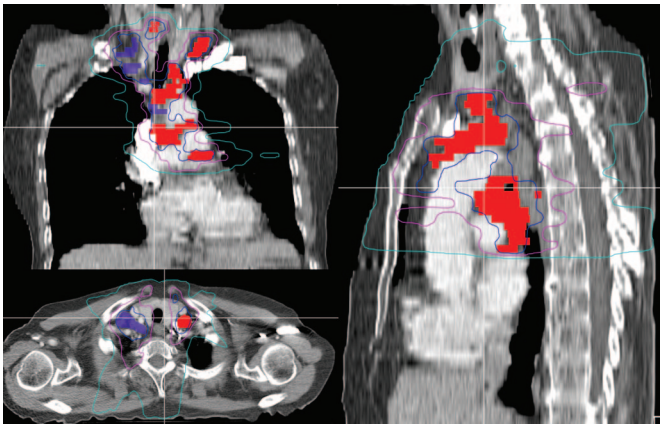

FIGURE 4. Other views of the IMRT plan from the second patient in Figure 3. The malignancy is represented in red and purple. The following isodoses are shown: 60 Gy (*blue*), 45 Gy (*pink*), and 20 Gy (*light blue*). This technique allows sparing of the normal tissues to a greater degree than standard field setup techniques such as the use of anteroposterior-posteroanterior and opposed oblique fields.

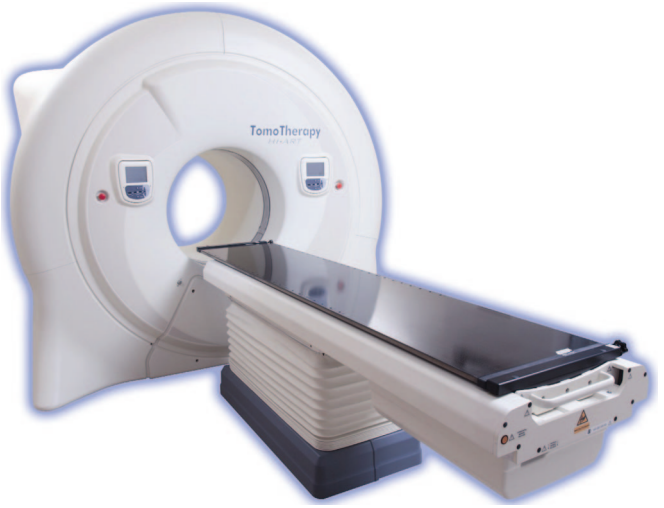

FIGURE 5. Tomotherapy unit. Helical tomotherapy includes IMRT delivered as the linear accelerator rotates around the patient in a continuous helix. This is performed with a linear accelerator mounted in a manner analogous to a CT scanner. (Provided by and reproduced with permission of TomoTherapy, Inc., Madison, WI.)

Tomotherapy

Helical tomotherapy includes IMRT delivered as the linear accelerator rotates around the patient in a continuous helix. This is performed with a linear accelerator mounted in a manner analogous to a computed tomographic (CT) scanner. Scrimger et al. evaluated the potential of helical tomotherapy compared with conventional three-dimensional field arrangements.[34] They compared plans generated for five patients with unresectable NSCLC delivering 60 Gy to the tumor volume. The lung V20 was reduced in all cases using tomotherapy (range, 17–37% reduction; mean reduction, 22%). The authors concluded that tomotherapy decreased the doses administered to the normal tissues and could allow the safe delivery of a greater dose to the tumor volume. One additional advantage of this unit is the ability to image the patient during therapy and evaluate the location of the tumor to prevent geographic misses. The term "image-guided RT" is used to describe this ability. Clinical studies are needed to further evaluate the potential of helical tomotherapy (Figures 5 and 6).

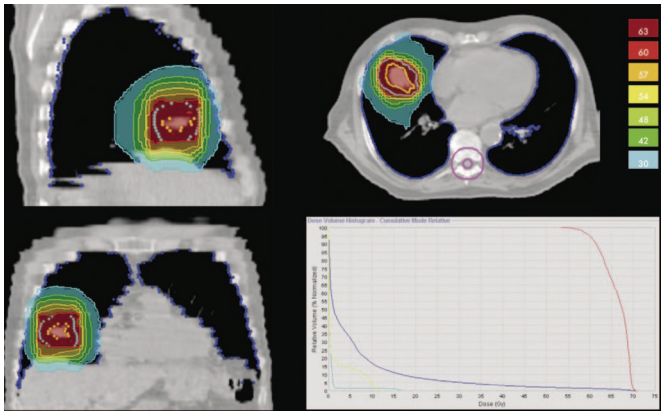

FIGURE 6. Dose-distribution from a plan treating using tomotherapy that shows a tight distribution of dose around the lung tumor. A dose-volume histogram is included at the bottom right. Doses are reported in gray. (Provided by and reproduced with permission of TomoTherapy, Inc., Madison, WI.)

Stereotactic RT

Stereotactic RT has been used to treat early-stage NSCLC with favorable preliminary results compared with historical data using conventional RT. Rowell and Williams[35] performed a detailed analysis of the historical results obtained with conventional RT for stage I to II NSCLC in patients unfit for or declining resection. The survival at 3 years ranged from 17% to 55% and at 5 years from 0% to 42%. Local failure occurred in 6% to 70% of patients.

In contrast to conventional RT, stereotactic techniques include fixation, ultraprecise treatment planning, RT directed to known disease alone, and high doses per fraction. Stereotactic RT has been most commonly used for tumors within the head.

Timmerman et al. reported a phase I trial that included 37 patients with clinical T1-2, N0, M0 NSCLCs (<7cm in diameter).[36] A stereotactic body frame was used to immobilize the patients that included an abdominal compression device to limit motion of the diaphragm. Seven noncoplanar, nonopposed beams were used to administer three doses—each of 8, 10, 12, 14, 16, or 20 Gy—2 to 8 days apart. The study was stopped at 20 Gy for three doses without determining an MTD, as only one patient suffered grade 3 pneumonitis. With a median follow-up of 15 months, six of the 46 (13%) have had local failures and the 15-month projected survival was 64%. No patient that received doses of greater than or equal to 18 Gy per fraction developed a local failure.

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On the basis of this experience, the RTOG has initiated a phase II trial (RTOG L-0236) for select patients with early-stage medically inoperable NSCLC.

Uematsu et al. reported a trial of stereotactic RT in 50 patients with T1-2, N0, M0 NSCLC.[37] They developed a fusion of CT and linear accelerator termed a FOCAL unit. The FOCAL unit is frameless and included a LINAC, CT scanner, simulator, and couch. Patients generally received 50 to 60 Gy in 5 to 10 fractions over 1 to 2 weeks. Eighteen patients also received conventional radiotherapy of 40 to 60 Gy in 20 to 33 fractions before stereotactic RT. With a median follow-up of 36 months, local failure occurred in three of 50 patients (6%) and nodal failure occurred in two of 50 patients (4%). The 3-year survival rate was 66%. No definite adverse effects related to stereotactic RT were noted, except for two patients with bone fractures and six with pleural pain.

Onishi et al. reported on 241 patients with stage I NSCLC treated at 13 institutions with tumors ranging from 7 to 58 mm (median, 28 mm) in diameter.[38] RT included noncoplanar dynamic arcs or multiple static ports delivering 18 to 75 Gy to the tumor in one to 22 fractions. With follow-up of 4 to 72 months (median, 18 months), pulmonary toxicity greater than grade 2 occurred in 2.1% and local failure occurred in 10.4%. A higher local failure rate was observed (20.0% versus 6.5%, $p = 0.04$) when the biologically effective dose was less than 100 Gy versus greater than 100 Gy. Regional lymph nodes and distant metastases occurred in 5.8% and 12.4%, respectively. The 3-year survival rate was 56.0%. On the basis of these results, they plan a phase II trial of stereotactic RT using 48 Gy in four fractions (biologically effective dose = 105.6 Gy) for patients with stage I NSCLC.

Whyte et al. reported a phase I trial of stereotactic RT for lung tumors (primary or metastatic) smaller than 5 cm in diameter using the CyberKnife system (Accuray, Sunnyvale, CA).[39] The CyberKnife is a frameless system that includes a 6-MV linear accelerator mounted on a computer-controlled robotic arm. It also uses IGRT technology with orthogonally mounted x-ray devices to observe and correct for movements of the bones and/or fiducial markers. Twenty-three patients received 15 Gy in one fraction using approximately 100 beam paths and respiratory tracking (Figures 7 and 8). There was a greater toxicity from the placement of fiducial markers (causing three pneumothoraces) than the RT (one pulmonary toxicity) (grade < 3). With a median follow-up of 7 months, there were two local failures and four deaths. They plan further dose escalation to 20 Gy and then 25 Gy.

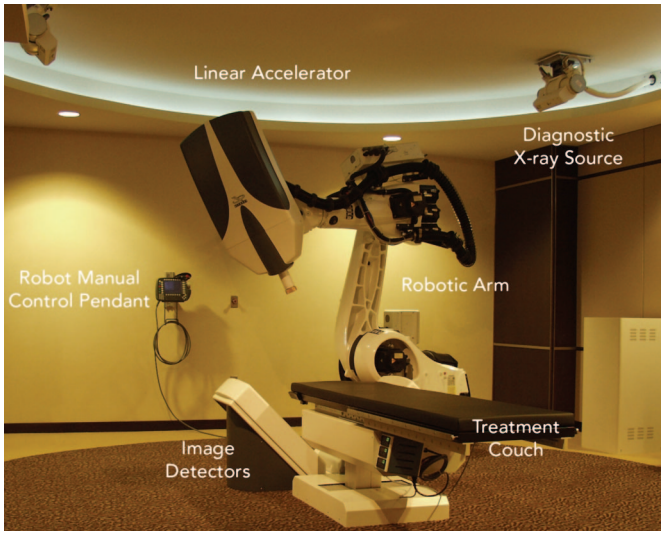

FIGURE 7. The CyberKnife. A linear accelerator is mounted on a computer-controlled robotic arm. Orthogonal x-ray cameras monitor movements that can be corrected for by the CyberKnife. (Provided by and reproduced with permission of Accuray, Inc.).

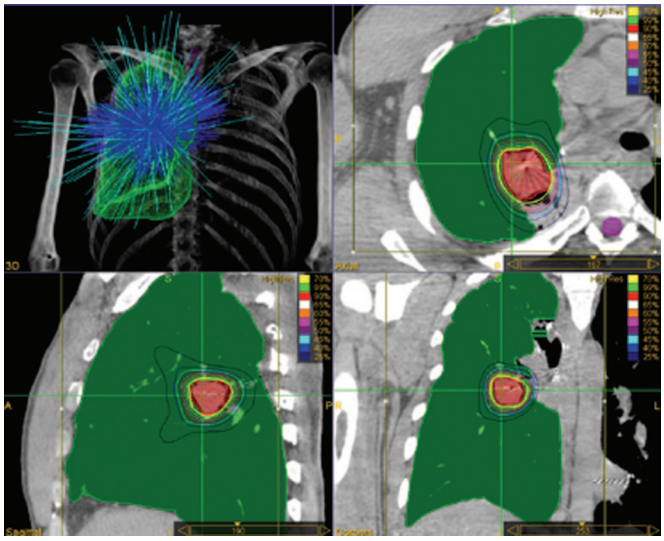

FIGURE 8. The CyberKnife used approximately 100 beams (*blue*) to treat this lung tumor. Isodose plots reveal a tight distribution of dose around the tumor. (Provided by and reproduced with permission of Accuray, Inc., and Dr. Lee McNeely, M.D.)

Hadron Therapy: Protons and Other Heavy Particles

A hadron is a subatomic particle composed of quarks that is influenced by the strong nuclear force such as a proton, neutron, or heavy ion. Potential radiobiological advantages of hadron RT compared with convention RT (x-rays and electrons) include higher relative biological effectiveness, higher linear energy transfer, lower oxygen enhancement ratio, and excellent dose distribution. Each particle has its own radiobiological characteristics. The major disadvantages of hadron therapy are the extremely high cost and complexity. Most of these beams exhibit a Bragg peak, except the neutron. This is a peak in the deposited dose that occurs in tissue at a depth very near the end of the particle's range. It is at this spot where the majority of the energy is deposited within tissue. The Bragg peak occurs at a specific depth based on the particle and the energy imparted on the particle by the acceleration system (Figure 9). The Bragg peak is generally so narrow that it is too small to cover most tumors. Thus, the

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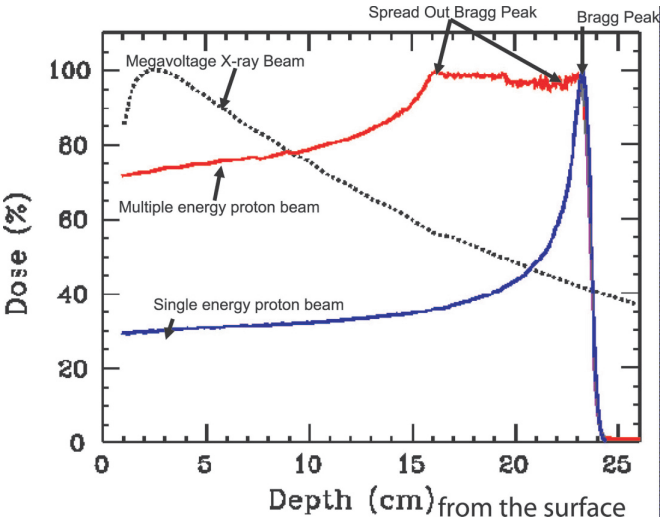

FIGURE 9. Depth–dose curves for three beams including a megavoltage (MV) x-ray beam (*dashed*), a single energy proton beam (*blue*), and a multiple energy proton beam (*red*). The MV x-ray beam peaks in dose deposition a few centimeters beyond the entrance point. The single energy proton beam enters the body, depositing a small fraction of the dose until it reaches the depth of the Bragg peak, and most of its dose is deposited in this very narrow range at a specific depth defined by the beam energy. Most tumors will not fit in this narrow Bragg peak. Therefore, the Bragg peak is spread out by using multiple energy protons, which make the beam clinically useful. This also results in an increased entrance dose (the dose near the patient's surface) of the beam compared with a single energy beam. The protons stop at the end of their range, yielding little, if any, exit dose. (Modified and used with permission of the Indiana University Cyclotron Facility. Available at: http://www.iucf.indiana.edu/Experiments/RadioBiology/papers/dose5.html.)

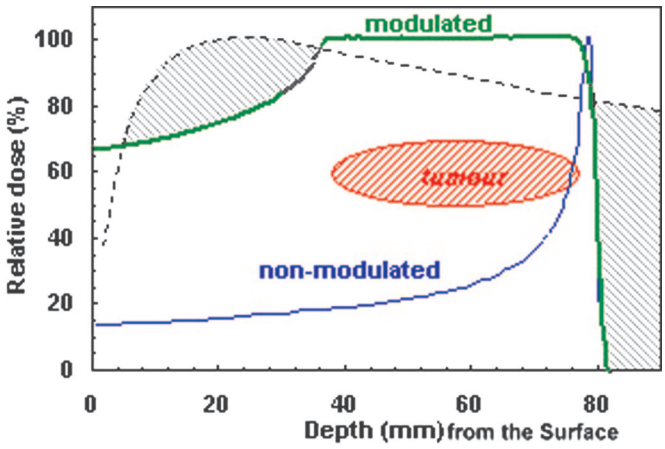

FIGURE 10. The same as in Figure 8. The same three beams' depth–dose curves are found: the x-ray beam is *dashed*, the single energy proton beam is denoted as "non-modulated," and the multiple energy proton beam is denoted as "modulated." A tumor is shown at a depth between 40 and 75 mm from the surface of the patient. The single energy proton beam does not provide adequate tumor coverage with dose because of the narrow Bragg peak. The modulated proton beam provides better tumor coverage in the spread out Bragg peak. The region of potential dosimetric advantage between the modulated proton beam and the x-ray beam is shown with *crosshatching*. (From the National Physical Laboratory, Teddington, Middlesex, United Kingdom. Available at: http://www.npl.co.uk/publications/news/ionrad/ionisingrad_issue13_pic01.jpg. (C) Crown Copyright 2005. Reproduced with the permission of the Controller of HMSO and the Queen's Printer for Scotland.)

Bragg peak must be spread out over an entire tumor's extent within the body. This is achieved with devices that alter the energy of the particles and create a beam of particles with varying energy and many Bragg peaks that, when added together, create a wider region of maximal dose encompassing the tumor (Figure 10). The process of spreading out the Bragg peak to make it clinically useful results in an increase in the entrance dose. One major advantage of these beams is the lack of an exit dose. Once the particle has been stopped in tissue, there is no further dose deposited beyond that point. In addition to a Bragg peak, carbon ions have an increased radiobiological effectiveness and thus a greater degree of cell kill for a given dose than either protons or conventional x-ray (photon) beams (Figure 11).

Bush et al. reported the Loma Linda experience treating unresectable stage I NSCLC patients treated with proton RT. The target included the gross tumor volume as seen on CT scan, with additional margin to allow for respiratory motion. Multibeam plans delivered 51 GyE in 10 fractions over 2 weeks to the first 22 patients; the subsequent 46 patients received 60 GyE in 10 fractions over 2 weeks. Sixty-eight patients were analyzed with a median follow-up of 30 months. There were no cases of symptomatic radiation pneumonitis or late esophageal or cardiac toxicity. The 3-year local control and disease-specific survival rates were 74% and 72%, respectively. There was significantly better local tumor control in T1 versus T2 tumors (87% versus 49%), with a trend toward improved survival.[40]

Miyamoto et al. performed two phase I/II trials with carbon ion therapy. All patients had stage I NSCLC and were treated at the Heavy Ion Medical Accelerator in Chiba.[41] The primary tumor was irradiated without prophylactic nodal RT. In the first study (9303), patients received 59.4 to 95.4 GyE in 18 fractions over 6 weeks. In the second study (9701), patients received 68.4 to 79.2 GyE in nine fractions over 3 weeks. Grade 3 lung toxicity occurred in 3.7% (3/81) and grades 2 to 3 lung toxicity occurred in 9.8% (8 of 81). Grade 2 toxicity occurred in three of five patients at the 95.6-GyE dose level in the first protocol and two of three patients at the 79.2-GyE dose level in the second protocol. These doses were considered the MTD for these particular dose-fractionation patterns. Local recurrence occurred in 19 of the 82 primary lesions (23%). The 5-year survival rate of all 81 patients was 60%. The 5-year survival was 64.4% for stage IA and 22% for stage IB. Local control was influenced by dose ($p = 0.03$). In the dose–response analysis of 9303, it was estimated that 4-year local control rates were 40% with 59.4 GyE, 55% with 64.8 GyE, 70% with 72 to 79.2 GyE, and 80% with greater than or equal to 86.4 GyE. The authors felt that the local

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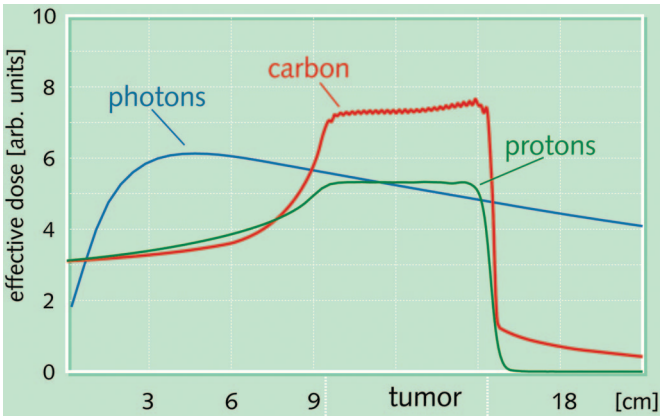

FIGURE 11. Effective depth–dose curves of three beams: photon (x-ray), carbon ion, and proton. The effective dose includes both the absolute dose and radiobiological effectiveness of the beams in killing cells. A tumor is denoted on the *x* axis at a depth of 12 to 15 cm from the surface of the patient. The photon beam delivers a greater proportion of its dose both superficial and deep to the tumor than the other beams. The carbon ion beam delivers a greater effective dose than the proton beam to the tumor for a given entrance dose. In addition, there is a slightly greater exit dose for the carbon ion beam than the proton beam. (Available at: http://www.gsi.de/portrait/Broschueren/Therapie/Krebstherapie_e.html. Reproduced with permission of Gesellschaft für Schwerionenforschung.)

control (77%) achieved with carbon ion RT was equivalent to surgical resection.

CONCLUSIONS

During the past three decades, there has been progress in the understanding of lung cancer, resulting in improvements in treatment and patient survival.[3] Radiation has a key role in treating lung cancer. Innovations include altered fractionation patterns, three-dimensional treatment planning, IMRT, tomotherapy, stereotactic RT, hadron therapy, and better systemic therapy. Recent studies suggest that newer techniques may enhance the outcome of patients with lung cancer by allowing the safe delivery of greater doses of RT. With regard to a simpler treatment innovation, TIDRT appears better than QDRT.

Chemotherapy has been shown to increase the survival of most patients with lung cancer. Systemic therapy is evolving to targeted therapy specific to molecular abnormalities present in an individual tumor. It is hoped that targeted therapy will yield better survival and less toxicity. More research is needed combining targeted agents with RT. We also need a greater understanding of the molecular events that take place in irradiated cells so that targeted agents can be designed specifically to improve the therapeutic index of RT.

Quite soon, we will be able to image a patient on the same device used to deliver ultraprecise high-dose RT. This device will need to correct for patient movement. All known disease including both local disease and metastases will be targeted and irradiated to huge doses, sparing normal tissues. These future RT systems may provide disease control more safely and effectively than resection. Innovations such as those described will only be possible with continued research.

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